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NEW METHODS OF DELEADING HEAVY LEAD ABSORPTION USING CALCIUM MONO SODIUM ETHYLENE DIAMINE TETRA ACETATE (EDTA)*

ELSTON L. BELKNAP, M.D.**

After dealing with this subject for thirty years, I still find new and unexpected types of lead exposure, non-industrial as well as industrial. In all cases the dosage, that is, concentration and duration of exposure, is important. For my own understanding and for that of others, each case should be analyzed from the point of view of lead absorption as distinct from lead intoxication. Evidence of lead absorption is shown by the demonstration of lead line, a few stippled cells 5 to 10 per fifty fields, coproporphyrin in the urine, and, when medical-legal need demands it, quantitative study of lead in the urine. These findings do not, however, necessarily spell lead poisoning.

Lead poisoning or lead intoxication occurs only when, in addition to the above mentioned findings of lead absorption, we have symptoms or signs of actual disability. These symptoms may be merely weakness due to a secondary anemia usually preceded by a rapidly rising stippled cell curve. Lead intoxication occurring in 90 per cent of the cases is that of typical abdominal lead colic associated with ever-increasing constipation. As a positive therapeutic test and in contrast to the acute surgical belly, such a lead colic is relieved rapidly by intravenous calcium gluconate. Lead palsy which occurs only one-tenth as often as lead colic is the second commonest type of lead intoxication. Treatment for this in the past has been rest of the affected part for several months.

The rarest type of lead intoxication in adults is lead encephalopathy. In children, however, it is the most common type and seems to be increasing. In the past, treatment has not been specific for lead encephalopathy in the child. In the majority of cases, the outlook has been poor, frequently resulting in death or a serious residual in the form of mental deterioration. However, with increased use of Calcium EDTA the outlook has apparently improved.

In the treatment of the commonest type of lead intoxication in the adult, namely, the lead colic, there are two aims (1) the immediate relieve of symptoms, and (2) ridding the system of absorbed lead by some type of deleading therapy after the acute symptoms have subsided. If we were merely scientific we would simply remove the individual from lead exposure, knowing that within a week or two the lead colic symptoms would subside spontaneously. However, such a strictly scientific form of therapy is inadequate.

Since introduced by Joseph Aub in 1926 calcium salts have been efficacious when given intravenously for the relief of lead colic. However, such relief by calcium gluconate seems to be due to the non-specific effect of calcium in relaxing smooth muscle, rather than an immediate clearing away of the lead by the calcium.

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*Presented before the Henry Ford Hospital Medical Association, Detroit, Michigan, Nov. 12, 1954.

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For actually ridding the system of absorbed lead by deleading there have been many different types of therapy suggested in the past 25 to 30 years. Clinicians have advocated shift of the acid-base metabolism, low calcium intake, high phosphorous diet with magnesium sulphate sodium citrate, and the long used potassium iodine type of therapy. However, no single method has been completely satisfactory. All have been questioned by a number of workers in the field. Certainly no such general agreement upon treatment for deleading exists as does for the relief of smooth muscle colic by calcium gluconate. Calcium Mono Sodium Ethylene Diamine Tetra Acetate, also called Calcium EDTA, Versene or Sequestrine, recently introduced, may be the deleading agent when given intravenously. Certainly it increases the urinary lead excretion markedly. To show how effective this new drug is in stimulating urinary lead excretion, we need only to note the previous levels in acute lead intoxication of about .3 to .8 mgs. lead per liter of urine lead, now raised 10 to 20 times this old excretory figure.

Let me emphasize that we are discussing the use of Calcium EDTA, not Sodium EDTA. Calcium EDTA seems to be harmless, though the sodium salt in much heavier dosage than I have used may produce a lower nephron nephrosis. Detailed blood chemistry and bone marrow studies of my hospital series showed no toxic effects from the Calcium EDTA except a slight transient bone marrow depression in 2 of 7 cases. In California, experimental work is being done as to possible toxicity of Calcium EDTA.

Publications on this subject began to appear about 1950. Reports on the subject from individuals and medical centers throughout the country have been increasing especially since 1952 and number about 80.

The theory of action of this new drug, Calcium EDTA, is that it chelates or binds a metal-ion like lead by complexing the metal in a ring structure so tightly that it is un-ionized. This apparently renders the metal harmless for safe excretion. Whether, however, such complexing will cause immediate relief of symptoms such as actual lead colic is still an open question. We do know that it is the most effective from of deleading that has yet been discovered either in the acute type of lead intoxication or the chronic type of lead absorption.

My hospital cases were treated with 5 cc. intravenously or one gram of Calcium EDTA diluted in 250 cc. of 5% glucose in distilled water over a period of 20 minutes twice a day for five days followed by a rest period of two days with a resumption of the five day course. This was followed by an additional period of rest for two days and finally a course of four days as before. Uniformly lead excretion went up and porphyrinuria went down. Some feel that this latter finding is most important because it may be an index of improved liver function slides.

My own experience covers about twenty cases in whom I used Calcium EDTA intravenously. Seven of these were under hospital control and showed no lasting residual. Thirteen outpatients who were workers having heavy lead absorption but no evidence of any disabling lead intoxication, were also studied. They were treated on a purely prophylactic and preventive basis supplemented by the reduction of lead exposure by increased engineering protective techniques installed by plant management. These 13 cases of extremely heavy lead absorption followed intense lead exposure due

to their work in smelting scrap battery plates. It was a small plant where engineering protection had, at that time, been entirely inadequate. It then seemed that the men would either have to be laid-off or hospitalized. Inasmuch as they had no symptoms, and management promised marked improvement in engineering protection, I felt it advisable to treat them intravenously with Calcium EDTA. All were given one to four courses of Calcium EDTA intravenously on the following modified schedule while at work and without symptoms. The men were sent to the company doctor's office one hour each day for five days a week. During the first part of the hour each man was given intravenously 5 cc. of Calcium EDTA in 250 cc. of 5% glucose in normal saline over a period of 20 minutes. He rested one-half to three-quarters of an hour and then returned to work. At no time did any man show untoward symptoms, and all insisted they felt better. The lead lines of the gums disappeared, and the stipped cells dropped markedly. Because these cases were studied while at work and were not under hospital control, it was impossible to study their 24 hour urine excretion. However, their urine porphyrin dropped rapidly and continued low just as in the 7 cases studied under hospital control.

In summary, these clinical cases seem to show that Calcium EDTA given intravenously is an excellent method of ridding the organism of lead by deleading, though in my experience it does not relieve lead colic promptly. My studies as well as other reports in the literature prove it to be superior to any previous deleading treatment and entirely safe.

One recent and detailed report of three cases treated with Calcium EDTA at the Massachusetts General Hospital, is that by Hardy[1]. All of Dr. Hardy's cases were subsiding lead intoxication, lead colic type cases, whereas two of mine were actually having acute lead colic. My experience in these two cases, moreover, tends to suggest that the intravenous Calcium EDTA will not relieve lead colic at once, though it certainly increases the urinary lead excretion. Immediate relief of symptoms can, therefore, be best obtained by supplementary calcium gluconate given intravenously in alternate doses with the Calcium EDTA.

Whether or not Calcium EDTA may be used prophylactically in the form of tablets for oral use in the cases of heavy lead absorption remains to be studied further. Such oral therapy is certainly not as effective as the intravenous form.

Experience in these 7 cases of heavy lead absorption treated under hospital control and the 13 cases treated in the doctor's office while at work, indicates that the intravenous Calcium EDTA is both effective and safe as a deleading agent. However, this is to be considered an emergency measure. Proper engineering protective devices which prevent lead exposure and resultant lead absorption are still the best treatment.

ADDENDUM September 10, 1956.

A detailed report of the 7 hospital cases referred to in this paper was presented before the American Medical Association June 22, 1954 and published in December 1954[2].

Since this time a number of other individuals have reported cases treated with Calcium EDTA with prompt and effective elimination of lead. However, Foreman[3] has

recently reported a case of a patient heavily loaded with plutonium whom he had treated with Calcium EDTA. He sounds a note of warning regarding nephrotoxic hazard from uncontrolled Edathamil Calcium-Disodium therapy. After a preliminary 5 gm. treatment of 4 days followed by two days rest, the drug was administered for another 12 consecutive days. This is definitely a more concentrated type of therapy than I have recommended. However, because plutonium is apparently more difficult to remove from the body than is lead, this therapy seemed necessary. His patient then showed evidence of apparent damage to the renal tubules though this was fortunately reversible.

Foreman then did further experimental work on rats treated daily for 16 days which led him to believe that 2.5% of patients given 9 grams of the drug a day for 16 days would be expected to develop nephrosis. However, he recommends the therapeutic dosage level of 5 grams a day given not more than 5 days in succession and followed by a two-day rest period as well within the desirable safety limits. The dose of 2 grams a day that I have used and found successful seems safe in the individual who does not already have evidence of acute or chronic renal disease.

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IMPRESSIONS OF THE XXth INTERNATIONAL PHYSIOLOGICAL CONGRESS

OLIVER H. GAEBLER.* Ph.D., M.D.

Among institutions which survive such tragedies as anarchy, dictatorships, and war, few can equal the record of religious and scientific organizations. The survival power of churches and universities requires no comment. International scientific meetings, likewise, proceed as usual after unavoidable interruptions.

The first meeting of the International Physiological Congress was held in Basel, in 1889. At 3 year intervals, thereafter, meetings were held in Liege, Berne, Cambridge (England), Turin, Brussels, Heidelberg, Vienna, and Groningen. World War I caused an interruption from 1913 to 1920, when the 3 year schedule was resumed with meetings in Paris, Edinburgh, Stockholm, Boston, Rome, Moscow-Leningrad, and Zurich. World War II intervened between the meeting in Zurich in 1938 and one in Oxford in 1947. Once again the 3-year schedule was reestablished. The Congress met in Copenhagen, Montreal, and most recently in Brussels, July 30 to August 4, 1956. The twenty-first Congress is scheduled to meet in Buenos Aires, in 1959, the council having accepted the invitation of Nobelist B. A. Houssay.

President of the XXth Congress was Professor Corneille Heymans, who, in 1939, was awarded the Nobel Prize in Medicine for 1938, in recognition of his studies of the carotid sinus and cardio-aortic receptor mechanisms in respiration. His father was likewise a distinguished pharmacologist and professor at Ghent, and a pupil of DuBois Reymond. Scientific meetings were held in large teaching auditoria of the University of Brussels. One entered by the Avenue Paul Heger, commemorating the "founder of recent Belgian physiology", who was born in 1846 and died in 1925. The opening session was held Monday afternoon, in the Palais des Beaux Arts, in the presence of Queen Elisabeth of Belgium. President Heymans announced that about 2500 representatives of 43 countries were present. By scanning representative pages of the membership list, the writer estimated that about 20 per cent were from the U. S. A.

The two address at the opening session were by Prof. C. H. Best, President of the International Union of Physiological Sciences, and Prof. Pierre Rijlant, Director of the Institut Solvay de Physiologie. Professor Best outlined the international organization which has taken form in recent years. This is a matter to which the officers of many scientific organizations throughout the world have devoted much thought and effort. The numerous international organizations in different areas of investigation have extensive liason with one another and with UNESCO. The function of these organizations is "to facilitate the interchange of productive ideas and plans". Arrangements for international meetings, and collaboration in the problem of abstracting the literature are among their principal problems.

The address of Professor Rijlant, entitled "The Future of Physiology", dealt with an aspect that would have appealed to any medical man, — the confusion of tongues

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that modern technology has wrought in so many fields that once were rather clearly defined. Thus the discipline "tends to split into numerous fragments whose subsequent development is centrifugal". However, the speaker recognized why this is inevitable: "It has become impossible for anyone, no matter how gifted, even to pretend to have appreciated all the implications of the overwhelming number and diversity of reports. Thought and knowledge obviously cannot hope to develop to fully creative levels unless the field of interest is sufficiently sharply delimited". Then he voiced the profound truth: "And yet there is a unity in life itself and its fundamental mechanisms and their manifestations which is to be found in the main features of the function of every organ." This basic fact, and the influence of great leaders, to which the speaker devoted much of the remainder of his address, gave him a basis for confidence that centrifugal forces would not overcome integrative ones.

Organization of the extensive scientific program left little to be desired. Each morning, Tuesday through Saturday, which was "pharmacologists' day", there were 15 to 16 separate sessions in which 7 to 15 papers, well grouped as to content, were presented. There were also programs consisting of films. During afternoons, with the exception of Thursday (reserved for excursions to Bruges, Ostend, or Antwerp) there were two to four symposia or special group meetings. Two evening receptions were held by representatives of the Belgian and city governments, and a superb program by the Belgian National Symphony Orchestra was presented Wednesday evening.

In keeping with quotations from Prof. Rijlant's address, no attempt will be made to review the scientific program in detail. The two books of abstracts contain 1604 pages, and the writer took many additional notes! The perpetual question: "Was anything truly outstanding presented?" may also go unanswered, for appreciation of individual contributions is largely a matter of one's immediate interest.

Several contributions may be mentioned as representative of general trends. In the development of medical knowledge, the study of structure, — gross anatomy, histology, and presently electron microscopy, — continues to be fruitful. "Electron microscopic studies on the islets of Langerhans of the adult guinea pig and dog", presented by P. E. Lacy, brought out a species difference (three types of islet cells in the guinea pig) and opened the way for granule counts in response to various stimuli. Similarly, a paper presented by B. Kisch, entitled "The contribution of electron microscopy to the physiology and pathology of circulation" emphasized the relatively huge content of enzyme containing sarcosomes in heart muscle as a clue to the ability of the heart to beat for a lifetime, and, in connection with problems involving capillary permeability, the finding that the capillary wall is not a sheet but a complicated structure.

In a symposium on "Physiology of water and food intake", the contribution of B. Andersson closed with a striking film showing that electrical stimulation of a small area of the hypothalamus caused goats to drink water in amounts up to 40 per cent of their body weight. The response began in about 5 seconds and ceased 2 to 3 seconds after stimulation ended. While "classical conditioning" was excluded, a lively discussion about "experimental conditioning" ensued. A paper entitled: "Hypothalamus, hypophysis, and thyroid gland," presented by G. W. Harris on Saturday afternoon typified the constant attempt of scientists to construct an overall pattern from isolated facts.

In this instance two questions were explored: (1) How are stimuli (cold, light, stress), or emotional disturbances to which they give rise, transmitted to the thyroid gland? Do they reach the thyroid directly, through nervous pathways from the central nervous system, or via hypothalamus and pituitary, or via other endocrine glands? (2) How does the "feed back" work? Where is the inhibitory action of secreted thyroid hormone exerted? Thyroid activity, in rabbits, was measured by the rate of disappearance of radio iodine from the gland, the log of residual radioactivity being linear with time in the absence of stimulating or inhibitory effects. The effects of hypophysectomy, stalk section, and other procedures were studied. Stalk section reduced thyroid activity, but not to the same extent as hypophysectomy. The stalk was necessary for transmission of emotional, but not for stressful stimuli, in keeping with Fortier's thesis, and was apparently not essential in the feed-back mechanism. That the pathway from hypothalamus to pituitary is vascular rather than nervous was again emphasized. The hypophyseal portal system of vessels is becoming as important in endocrinology as another portal system is in gastroenterology.

A final comment may be made about the titles of programs. Many of them dealt with the function of organs or systems: salivary glands, gastrointestinal tract, pancreas, striated muscle, smooth muscle, heart and circulation, sympathetic nervous system, central nervous system. Others dealt with well-known processes, — blood clotting, photosensitivity, thermoregulation, active transport, or metabolism in general. Still others were oriented toward hypertension, inflammatory reactions, stress, hypothermia, epilepsy, effects of radiation, and cancer. On "pharmacologists' day" neuropharmacology of course received much attention. Whenever investigators of sufficient calibre are brought together one will have a worthwhile scientific program, regardless of title.

ACTINOMYCOSIS — CEREBRAL INFECTION PRESENTING AS A BRAIN TUMOR

W. E. Rush, M.D.*, J. P. Truant, M.D.**, J. C. Sieracki, M.D.**
and G. Manson, M.D.*

INTRODUCTION

Actinomycosis is an uncommon disease in any age group. It is particularly unusual in children, being accorded only brief discussion in a current textbook of pediatrics[1] and is not discussed in recent pediatric literature. Ordinarily, the disease appears in any of several well-defined forms; the cervicofacial type, as a chronic pulmonary infection or as an indolent bone infection. In most patients only one of these types usually occurs. The present case is reported because of the peculiar presenting symptomatology and also because of the co-existence of pulmonary and cerebral lesions due to Actinomyces bovis (Israeli).

The patient was a 13 year old white male with the chief complaint of anorexia, weight loss for three months and vomiting the past two days. He was well until approximately two months prior to admission at which time he had several attacks of abdominal pain associated with vomiting and headache and leg pains. He was admitted to another hospital where an appendectomy was performed, and the patient was discharged being told that he had rheumatic fever. After discharge the patient continued to complain of headache, nausea and vomiting with pain in varying joints. He had had a progressive weight loss, losing a total of approximately 20 pounds. He had had no chorea, no subcutaneous nodules, no particular tachycardia. Two days prior to admission the patient began to have marked nausea and projectile vomiting associated with a fever. The day of admission his temperature was 101 degrees, and he had had a drenching sweat the night before.

The past history was that at the age of 2½ years the patient had a blow on the head after falling out of a truck with no known unconsciousness. He had had routine immunizations and had had the usual childhood diseases. There was a maternal aunt who died of tuberculosis with whom the child had no contact. There was no family history of allergy, thyroid disease or convulsions. There are four siblings, all in good health. One year prior to this admission the child had a severe respiratory infection said to be "almost pneumonia". Child lived with his father in a rural area. The parents have been divorced for several years.

Physical examination on admission revealed a well developed, poorly nourished white male who appeared chronically ill. He was slightly pale. His temperature was 101, pulse 141, respirations were 28 and a blood pressure of 92/70 was obtained. Examination of the head revealed a normal shape and contour with closed fontanels. The ears revealed intact tympanic membrane with clear canals. There was no gross defect in hearing. The eyes revealed round and equal pupils which reacted to light

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and accomodation, the sclerae were clear and extra ocular movements seemed normal. There was a question of some blurring of the disc margins. The nose was negative. The mouth revealed normal teeth in good repair, normal tonsils and a clear pharynx. The neck revealed some pain in the back on slow flexion but there was no rigidity. The chest was clear to auscultation and percussion. The heart revealed questionable enlargement to the left. There was an irregularity in rhythm with a pulse rate of 140. There was a harsh systolic murmur heard over the entire pre-cordium but heard best in the third innerspace at the left mid-clavicular line. Femoral pulses were palpable. Examination of the abdomen revealed no masses. There was a right lower quadrant recent scar, and there was no tenderness. The back revealed definite costo-vertebral angle tenderness on the right. Neurological examination revealed very active, but bilaterally equal, deep tendon reflexes. There were no pathological reflexes and sensorium was clear. The initial impression was that of rheumatic heart disease with possible auricular fibrillation, and brain tumor was to be considered.

Laboratory studies obtained on the day of admission revealed a sedimentation rate of 34, a normal urine, 10.2 grams of hemoglobin, 9,600 white cells with 77% polymorphonuclears and 23% lymphocytes. There were a negative Kline and a negative blood culture. Blood agglutinations were negative for typhoid. The initial chest x-ray revealed an aorta of normal size with moderate hilar enlargement. Bronchial vascular markings were reported to show a fairly normal distribution. There were several somewhat rounded areas of infiltration in the lower portion of the right lung field. There were areas of lessened density in the center of these nodules suggesting the possibility of cavitation (Fig. I). No bony destruction was seen, and the lateral revealed a normal spine. X-ray of the skull revealed no evidence of fracture or increased intra-cranial pressure. There were no abnormal densities or areas of erosion. Cautious lumbar puncture was done without difficulty and colorless fluid obtained. The laboratory examination of the spinal fluid revealed sugar of 47 milligrams percent, a protein of 150 milligrams percent and a chloride of 762 milligrams percent. There were 222 white blood cells, mostly mononuclears in the spinal fluid. Spinal fluid culture failed to yield any growth of organisms.

The patient's hospital course did not change over the next three days. There was a presistence of the frontal headache with vomiting, and careful neurological three days after admission revealed a cerebellar type ataxia of the right arm and leg with questionable deviation of the tongue to the left and no definite papilledema. There were no pathological reflexes. Repeat blood count revealed 10.5 grams of hemoglobin, 4,200 white blood cells, 90% polymorphonuclears, 10% lymphocytes. The N. P. N. was 32 milligrams percent and fasting blood sugar was 92 milligrams percent. A smear seen in special hematology revealed normal cell morphology. An OT of 1 milligram was also negative. He was started on chloromycetin and sulfadiazine. He died suddenly on the tenth hospital day, the day prior to scheduled ventriculograms. An EEG was not obtained.

Discussion: This seriously ill boy was admitted to the hospital with a combination of symptoms and findings suggestive of chronic infection over at least a two or three

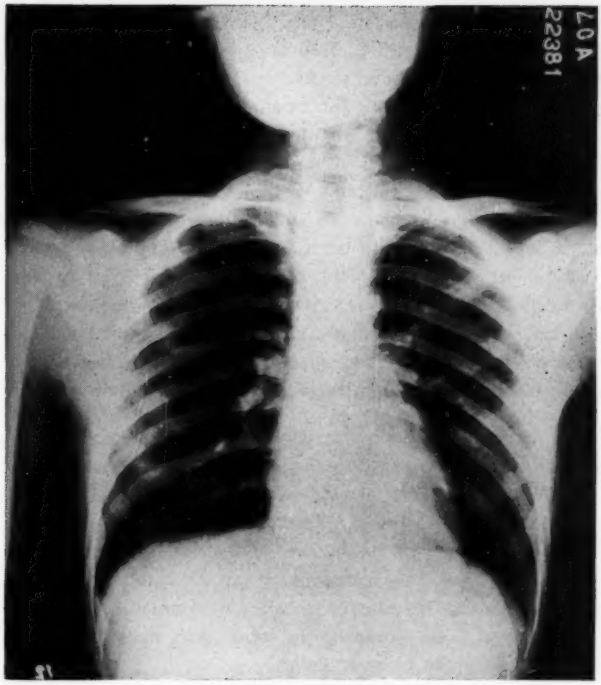

Figure 1
"There is a cavity in the right lower lung with some parenchymal infiltration laterally."

month period with localization in the lung fields and in the central nervous system. The findings in the spinal fluid coupled with the physical findings on neurological examination suggested an infection of the meninges and/or localized infection of the brain itself, that is abscess or encephalitis. The nature of the spinal fluid, that is mononuclear cells and a markedly elevated protein coupled with a normal cerebral spinal fluid sugar suggest a tuberculous infection. If this were a more acute bacterial abscess or chronic meningitis we would expect the spinal fluid protein to be much lower and the cell count itself to be higher. The infection would have presented with polymorphonuclears earlier, but it could concievably have shifted to a more chronic inflammatory cell picture at this time. The fact that the culture was negative on routine laboratory methods is, of course, against the more common bacteria and again suggestive of an acid fast organism. To reach a decision as to organism when one looks at the chest x-ray it becomes again very difficult. The lung picture could be compatible with tuberculosis and cavitation, but it does not rule out a bacterial abscess and chronic pneumonia. It is certainly conceivable with the laboratory and physical findings that the sequence of events was that of a pulmonary infection perhaps starting with the "almost pneumonia" one year ago and manifesting iteslf in acute fashion. When examining more closely the peripheral blood smear, a white count of 9,600 with 77% polymorphonuclears is definitely not suggestive of a bacterial

pulmonary abscess. It is, however, not very significant nor suggestive of tuberculosis. The OT being negative is at least a definite point against tuberculosis, but if this child is as acutely ill as the picture seems to be he could be relatively anergic and unable to respond to the skin tests. The heart, which can not be ignored, presented patholigical findings as indicated here, and it is possible that the child has had rheumatic fever and contracted this other chronic illness. It is possible, however, that this heart is one presenting subacute bacterial endocarditis, the multiple bacterial emboli accounting for the many abscesses in the lungs and brain. The blood cultures being negative are not helpful in this diagnosis nor are they against it. The peripheral blood count should be somewhat more elevated than it is, however, in subacute bacterial endocarditis. The spleen was not enlarged, and if this child were putting out multiple emboli you would certainly expect to find a spleen filled with emboli. It is possible, however, in trying to explain the heart findings that this represents only a functional murmur and that there is no significant pathology in the heart.

In summary we have a young boy with negative tuberculin skin tests, a non-descript peripheral blood picture and a definite abnormal chemistry to the spinal fluid, who presents himself with marked generalized disease symptoms, pulmonary abscesses and central nervous system symptoms. The most likely thing would appear to be a primary pulmonary abscess with secondary spread to the central nervous system, either in the form of encephalitis, meningitis or most likely abscesses. In spite of the negative tuberculin test and because of the non-inflammatory type blood picture, I would believe that tuberculosis would be the most likely cause and the over-whelming nature of it accounting for the ultimate demise.

DISCUSSION OF PATHOLOGIC FINDINGS

At autopsy this boy showed bilateral pulmonary abscesses, the largest of which measured 4 cm. in diameter. The brain showed numerous abscesses, up to 3 cm. in diameter scattered through the cerebellum. The purulent material was greenish-yellow. No definitive granules were seen. There was some generalized cerebellar edema with some flattening of the convolutions of the brain.

Laboratory examination of the pus revealed an organism with the cultural and morphological characteristics of Actinomyces bovis (Israeli). Microscopic examinations confirmed these gross findings, and numerous actinomycotic granules were found in the abscesses of the cerebellum and the lungs. While there was some perivascular cuffing in other portions of the brain, these were of a chronic and secondary nature. The meningitis appeared to be of a subacute variety. No granules were found in the meninges.

Figure II shows the presence of the actinomycotic granule in the upper right hand corner of the figure. It is surrounded by numerous polymorphonuclear leukocytes and a few eosinophils. In the lower left hand portion of the microphotograph, the normal folia of the cerebellum can be seen.

Figure III is a close up of a Gram stain of one of the actinomycotic granules found in one of the abscesses. (H. & E. 250x)

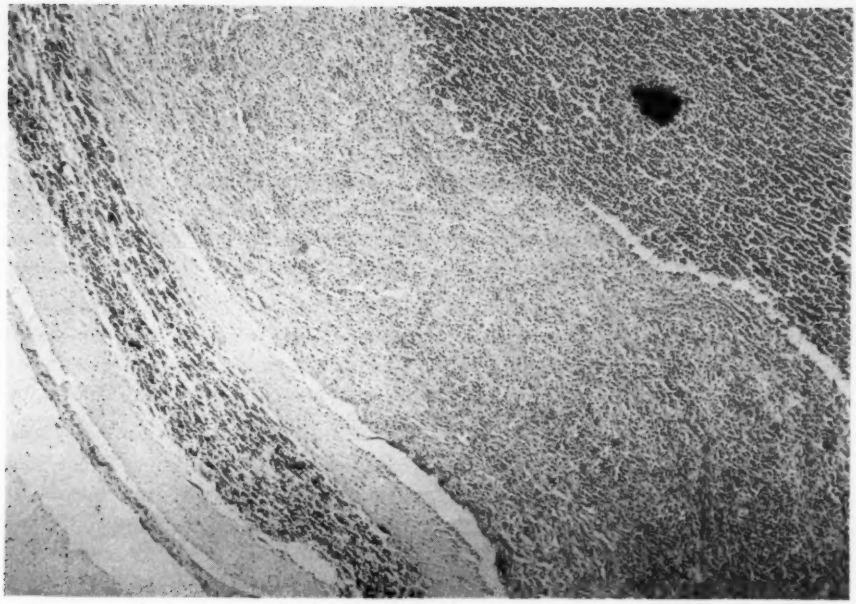

Figure 2
Actinomycotic Granule in Cerebellar tissue.

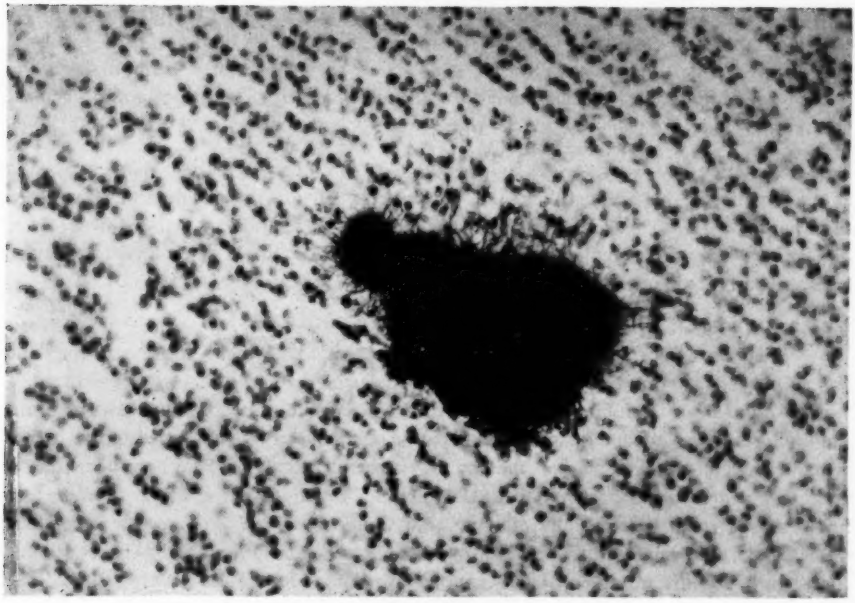

Figure 3
Actinomycotic Granule from the Abscess.

DISCUSSION OF THE BACTERIOLOGICAL FINDINGS

The actinomycetes are a varied group of filamentous microorganisms with some characteristics common to bacteria and fungi. The organisms range from the strict parasitic anaerobic actinomyces to aerobic non-pathogenic types. The members of this group which have medical interest are the anaerobic *Actinomyces bovis* and *Actinomyces israeli*. The former is responsible for actinomycosis in bovine species and the latter produces the disease in man. Although there are differences among strains of anaerobic *actinomyces* isolated from man and cattle, the single species *Actinomyces bovis* is considered by many investigators to be the etiologic agent of actinomycosis.

Since *actinomyces* are found in the tartar of teeth, in the crypts of tonsils as well as on various mucous membranes, a postive smear or culture from these sites does not necessarily indciate actinomycosis. Therefore, it is of paramount importance that the pus or exudate be collected aseptically, preferably from closed lesions by aspiration with a sterile needle and syringe after adequate disinfection of the skin.

Fresh preparations should be examined for gram-positive, branching, filamentous organisms. These structures are not acid-fast, do not form spores and are nonmotile. The filaments are usually slender (1 micron or less in width) nad have a marked tendency to fragment into bacillory forms.

Since gram-strained smears do not differentiate *Nocardia* from *Actinomyces bovis* the specimen should be cultured both aerobically and anarobically on suitable media, and the cultures identified by various criteria. Growth of *Actinomyces* appears at 37•C in from three to six days. Colonies can be picked from the agar or broth cultures and examined under a coverslip. The organisms are seen as tangled masses of delicate branching hyphae, or small fragments. Smears stained by Gram's method show the fungus to be gram-positive and small fragments frequently give the appearance of diphtheroids.

Inoculations of actinomyces into guinea pigs, rabbits or other animals by any of the common routes frequently produce no effect. Several investigators have reported that the suspension of pure cultures in 5 per cent hog gastric mucin induced progressive disease in white mice when inoculated intraperitonelaly. Others were able to produce actinomycosis in hamsters by intraperitoneal injection of pure culture.

TREATMENT

While the cerebeller lesions of this patient seem to have precluded survival, and indeed evaded ante-mortem etiological diagnosis, astinomycosis of more usual lacalization is responsive to combined therapy. This treatment should include intensive multiple antibiotic therapy, adequate surgical extirpation, or incision and drainage where anatomically possible, and radiation therapy of moderate dosage. Procaine penicillin is recommended in doses of 600,000 I. U. daily for a period of ten days. Sulfadiazene has been shown to be especially effective and should be given concurrently in divided doses of 4.0-6.0 gms. daily until improvement occurs and then should be continued for several months in doses of 2.0 gms. daily. Such dosage levels are suitable for all but the smallest of children. More recently broad spectrum antibiotics such as the tetracyclenes have been reported to give very favorable results[2]. The current

edition of Topley and Wilson[3] states the in-vitro sensitivity of the organism has been found to be, in descending order of sensitivity; penicillin, terramycin, choloromycetin, aueromycin and streptomycin. Inorganic iodides, formerly thought to have specific antimycotic action, are no longer regarded as being of value in the management of the disease. Finally, surgical excision or incision and drainage is essential where feasable. Sinus tracts, a common problem in the more usual forms of the disease, should be irrigated with 1% gentian violet solution. Lugol's solution has been used for this purpose but is likely to produce toxic side effects due to absorption of large amounts of iodine by the patient. This combined approach to treatment may be expected to result in a substantial recovery rate.

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THE EFFECT OF THE ADMINISTRATION OF THE ANTICOAGULANT MARCUMAR ON THE BLOOD COAGULATION MECHANISMS

SHIRLEY A. JOHNSON, Ph. D.*, M. JUNE CALDWELL, B.A. AND EDWARD MCCALL PRIEST, M.D.**

The coumarin type anticoagulants are considered to decrease the plasma levels of prothrombin and of one other plasma protein related to the coagulation mechanisms, autoprothrombin I (factor VII)[1]. Autoprothrombin I is believed to drop under the influence of these drugs before the prothrombin levels begin to fall. However, the time lag between the changes of each factor varies with the anticoagulant. Recently, however, Verstraete 1954[2], Sise, Kimball and Adamis 1955[3], and Johnson and Seegers 1955[4], reported a decrease in the plasma levels of autoprothrombin II (Christmas factor, Plasma Thromboplastin Component) following the administration of some of these anticoagulants.

Therapeutic anticoagulant administration is controlled by the Quick one-stage prothrombin time. This test is influenced by two of the three factors which we know the anticoagulants alter, but not by all three. There is no known test that will measure changes in all three factors simultaneously with any appreciable accuracy. The Quick prothrombin time is still probably the single, most useful, test to use. Nevertheless, hemorrhage has been observed in patients with a prothrombin time reduction to only 30-40 per cent of normal according to the Quick test. This discrepancy between laboratory findings in anticoagulant control and clinical observations could be due, at least in part, to changes in plasma levels of autoprothrombin II which are not observed in the laboratory using this one routine test.

An effective anticoagulant, which does not affect the plasma levels of autoprothrombin II, might well be the safest and easiest anticoagulant to control. Marcumar is an effective anticoagulant. Control of anticoagulant effect by marcumar is noticeably smoother than with other anticoagulants. This characteristic suggested an absence of effect on autoprothrombin II and led to this present investigation.

The role of the various factors which influence the Quick prothrombin time, in thrombotic disease, has not been fully delineated. It is possible that while the levels of two factors are measured usually during anticoagulant therapy, the beneficial effect

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of the therapy may be due to the reduction or change in the level of yet another factor. The results reported here do give us some understanding of the ease of control of one drug by the usual laboratory procedures.

METHODS

The methods used in this study have been described elsewhere, and are only briefly mentioned here.

One-stage prothrombin time: This method was described by Quick[5].

Two-stage prothrombin determination: Ware and Seegers described this test modified from that of Warner, Brinkhous and Smith[7].

Two-stage autoprothrombin I test: This test was developed by Seegers, Johnson and Penner[8].

Two-stage autoprothormbin II test: This test was first described by Johnson and Seegers[9].

RESULTS

THE PLASMA PROTHROMBIN LEVELS: In about half of the patients followed under Marcumar therapy, the two-stage prothrombin values did not change during the first twenty-four hours of therapy. However, in all ten patients the prothrombin values had dropped on the second day, and all had fallen by the fourth day to 50 u/ml. or below.

THE AUTOPROTHROMBIN II LEVELS: Unlike the anticoagulants studied previously Marcumar does not reduce the plasma and serum levels of autoprothrombin II. The cases were followed for at least fifteen days, and in some cases as long as twenty-eight days and the autoprothrombin II levels remained the same throughout. There is considerable variation in these levels before therapy. In one case, with myocardial infarction, no autoprothrombin II was found in the serum before therapy began.

THE AUTOPROTHROMBIN I LEVELS: These levels fell in the first day in every case. The fall in autoprothrombin I always preceded the fall in prothrombin or coincided with it. As has always been the case, the values for this factor were found to be higher in serum than in plasma.

DISCUSSION

Since Marcumar has been found to decrease the plasma levels of autoprothrombin I and prothrombin, but not autoprothrombin II, the significance of this latter component in the treatment of thrombosis can be considered. It is known that autoprothrombin II is deficient in patients with hemophilia B[10,11]. One of our patients sustained a myocardial infarction in the face of an absence of autoprothrombin II. There was no history of hemorrhagic tendency in this case. The anticoagulants Dicumarol, Hedulin, Tromexan and Sintrom all may reduce the autoprothrombin II level to practically zero without patient hemorrhage[12]. Conversely, patients may hemorrhage when the determined prothrombin time is not sufficiently reduced to account for this, and it has been postulated that a reduction of autoprothrombin II may be the explanation for this undesirable effect. Marcumar produces a reasonably stable anticoagulant effect as measured by the Quick prothrombin time. This observation is enhanced by clinical experience[13]. Numerous reports attest to Marcumar as an effective anticoagulant[14,15,16]. Since autoprothrombin II is not reduced by this drug, it is possible that its reduction is not necessary for effective anticoagulation therapy.

There is another consideration to bear in mind. It has been suggested by O'Brien that autoprothrombin II may have a prosthetic group which is phospholipid in nature[17]. This offers a possible connection between the lipids of blood and the coagulant mechanisms in the problem of thrombosis. The part played by this factor autoprothrombin II on the thrombosing tendency is very obscure and difficult to evaluate. Considerably more time will need to elapse, in all probability, before the study is complete.

CONCLUSIONS

The changes in the plasma levels of the pertinent components in the blood coagulation mechanisms have been studied in conjunction with the administration of the anticoagulant, Marcumar. This drug, Marcumar, does not alter the plasma levels of autoprothrombin II (PTC, Christmas factor) as does Dicumarol, Tromexan, Hedulin or Sintrom. The findings may account for the observation that anticoagulant therapy can be easily controlled with Marcumar as the Quick prothrombin time is the commonly used laboratory test under these circumstances, and this test is not influenced by different levels of autoprothrombin II. The concepts involving autoprothrombin II in the formation of intravascular thrombosis are viewed.

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THE ELECTROCARDIOGRAM IN INTERATRIAL SEPTAL DEFECT*

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Strictly speaking, it seems unlikely that the mere presence of an interatrial septal defect, unless it were very large or located in such a position as to involve the atrioventricular conduction system, could of itself be productive of any specific electrocardiographic pattern. Rather it would seem that any electrocardiographic abnormalities observed in the presence of this defect are more likely the result of changes in cardiac chamber work, and therefore size, coincident to changes in pressure and the direction (and volume) of blood flow across the defect in the interatrial septum. The primary diagnostic contribution of the electrocardiogram is therefore dependent on the accuracy with which it provides evidence not only of the presence and degree of single or combined cardiac chamber enlargement but also of the underlying hemodynamics and therefore the type of chamber enlargement observed.

Since mean pressures are normally higher on the left or systemic than in comparable positions on the right or pulmonary side of the central circulation, the direction of blood flow through an uncomplicated interatrial septal defect is from left to right. As a result the characteristic features are:

1. Increase volume flow of blood through the right atrium, right ventricle, and pulmonary circulation.
2. Increased work, without significant changes in pressure, and therefore increased size of the right atrium and right ventricle—in other words, those chambers receiving the increased volume due to the shunt.
3. Absence of systemic arterial oxygen unsaturation.

The characteristic electrocardiogram in uncomplicated defects of the interatrial septum is accordingly one representative of right atrial and right ventricular enlargement, the latter of the type designated as predominantly dilatation or diastolic-overloading (increased volume flow-work) enlargement in contrast to systolic-overloading (increased pressure-work) hypertrophy of this chamber. The typical pattern of this type of right ventricular strain and enlargement appears to be one of some degree of right bundle branch block. (Figures 1, 2 and 3). This immediately calls to mind several basic problems relative to the interpretation of bundle branch block patterns, which can be listed but not discussed within the time limits of this paper:

1. The importance of the factors of age and changing relative right ventricular mass in the genesis of various "typical" patterns of incomplete and complete (uncomplicated) right bundle branch block.
2. Electrocardiographic criteria for the determination of the degree of right ventricular enlargement in the presence of otherwise uncomplicated right bundle branch block.
3. The differentiation of patterns of right bundle branch block with and those without associated or complicating increased pressure-work hypertrophy of the right ventricle.
4. The recognition, in the presence of right bundle branch block (with or without right ventricular enlargement) of associated strain and enlargement of the left ventricle.
5. The determination of right ventricular enlargement in the presence of left bundle branch block. (Figure 4)

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**Division of Pediatric Cardiology.
All illustrations will also appear in the author's "Atlas of Electrocardiography in Congenital Cardiovascular Disease", Springfield, Ill., C. C. Thomas, In Press.

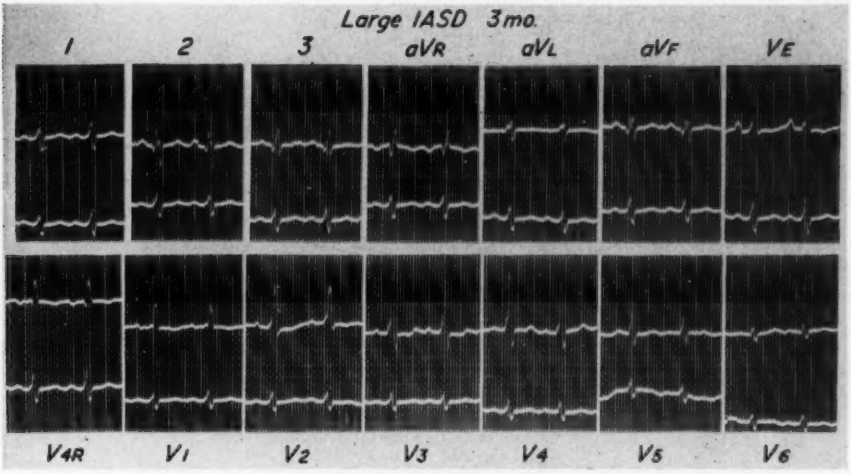

Figure 1

A typical electrocardiogram in an infant with a large uncomplicated interauricular septal defect. The precordial leads are characteristic of probable right bundle branch block and right ventricular hypertrophy. In this case there was fairly marked pulmonary artery and right ventricular hypertension.

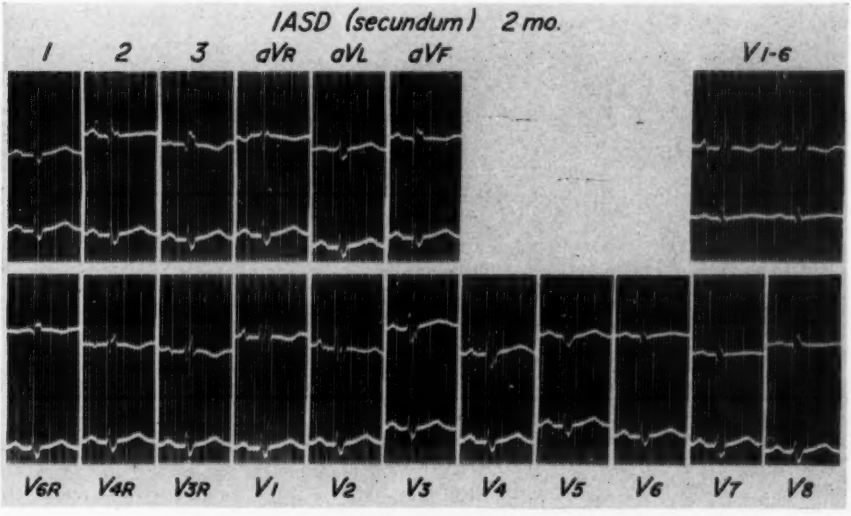

Figure 2

A typical electrocardiogram in an infant with an interatrial septal defect but no significant pulmonary artery or right ventricular hypertension. These precordial leads show uncomplicated right bundle branch block.

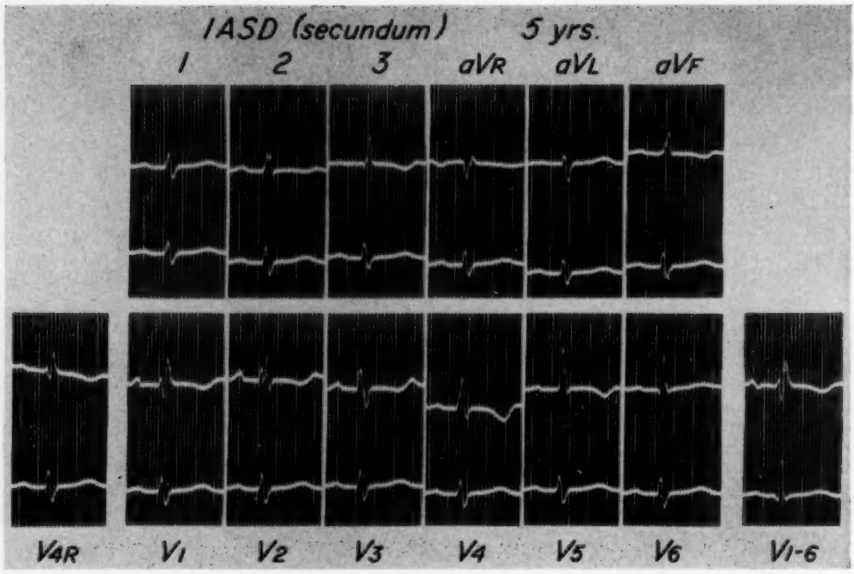

Figure 3

Another typical electrocardiogram in uncomplicated interauricular septal defect. T wave inversion across the precordium through lead V 5 is suggestive of marked right ventricular dilatation.

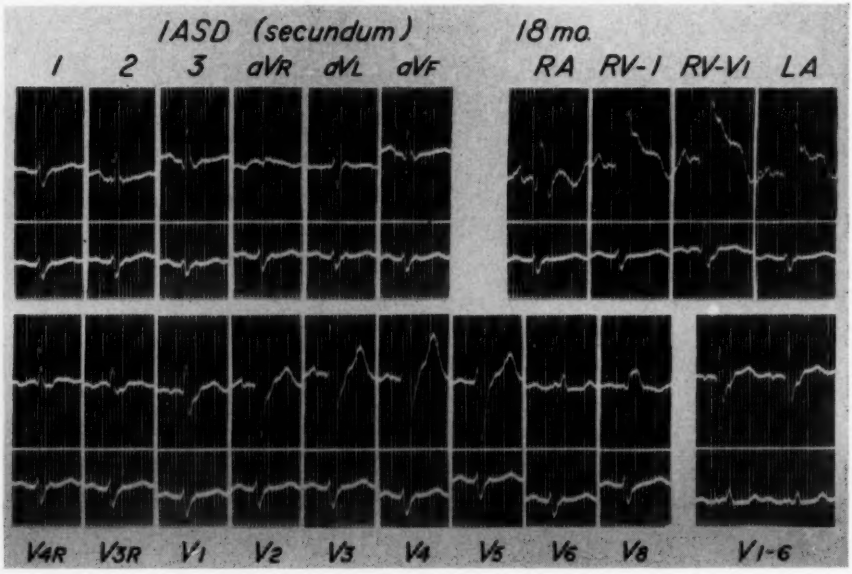

Figure 4

In this case there was an uncomplicated interauricular septal defect, proved surgically and by pre and post-operative cardiac catheterization. This is one of the extremely rare circumstances in which such a defect is associated with left instead of right bundle branch block.

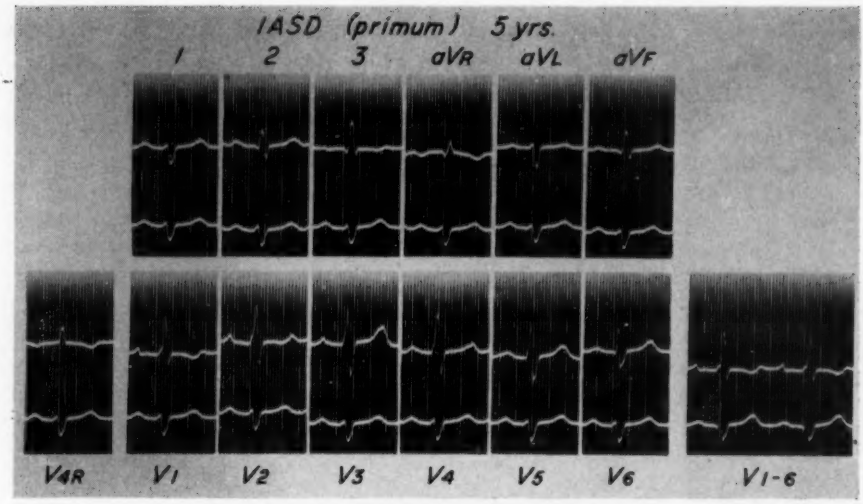

Figure 5

The electrocardiogram may or may not help in identifying the anatomic position of the interauricular septal defect. In this case, for example, there is no "typical" left axis deviation, nor definite evidence of associated left sided enlargement as seen with complicating mitral insufficiency. In other words, the electrocardiogram by itself does not necessarily exclude the possibility of a primum type of defect.

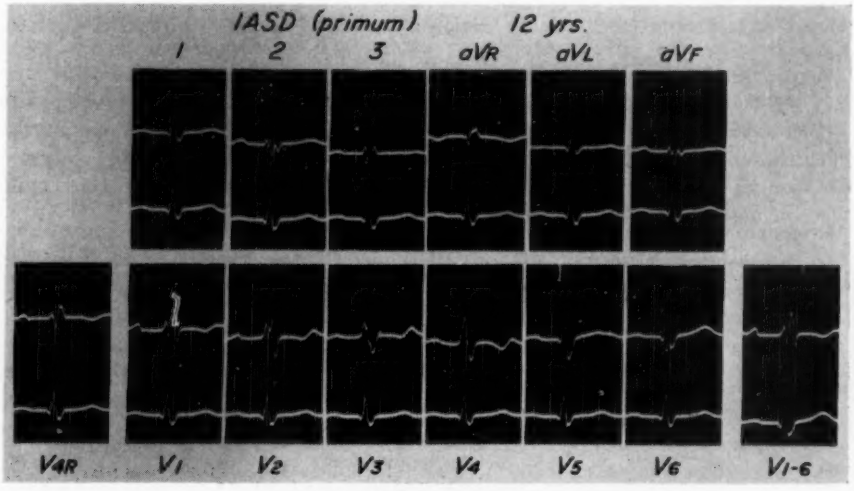

Figure 6

This is a more typical electrocardiogram in a primum type of interauricular septal defect—with left axis deviation in the extremity leads, and combined right bundle branch block and left ventricular hypertrophy in the precordial leads.

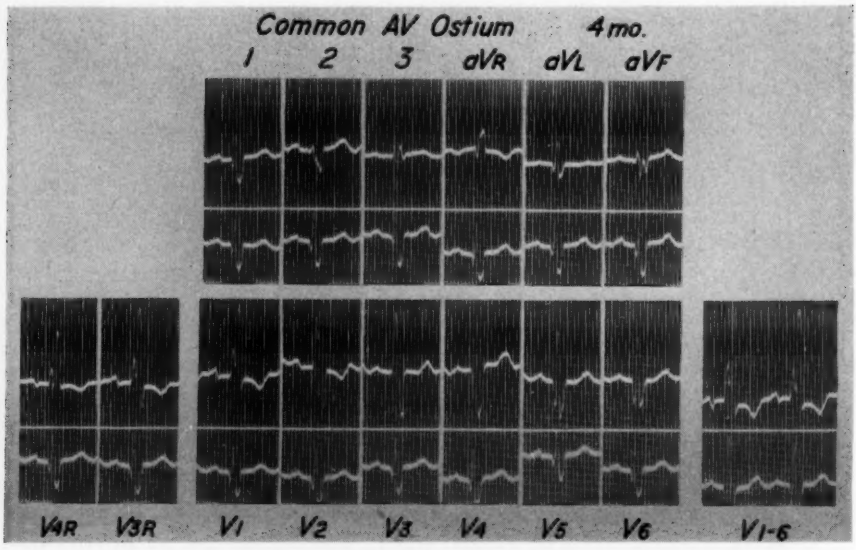

Figure 7

This is a typical electrocardiogram, especially the precordial leads, for combined right and left ventricular enlargement, of a type not observed in uncomplicated interauricular septal defect. This is much more characteristic of a high pressure communication and shunt, or a combined high and low pressure communication and shunt such as common A-V ostium.

It should be stated at this point that electrocardiographic criteria providing a solution to several of these problems are already available, while the others are the subject of current investigation, the completion of which may be expected in the near future.

On the basis, then, that the electrocardiogram provides detailed physiologic as well as anatomic information, it may be expected to contribute significantly toward the clinical clarification of problems representing major modifications of the otherwise simple hemodynamic pattern of an uncomplicated interatrial septal defect. Three basic types of modifications might be listed to include:

1. Obstruction to right atrial or right ventricular outflow, resulting in equalization or reversal of the usual pressure gradient and direction of shunt across the interatrial defect.
   a. Pulmonary hypertension
   b. Pulmonary stenosis
   c. Tricuspid stenosis or atresia

2. Obstruction to left atrial or left ventricular outflow increasing the magnitude of the usual pressure gradient and volume of blood flow across the interatrial septal defect.
   a. Coarctation of the aorta
   b. Aortic stenosis
   c. Subendocardial fibroelastosis
   d. Mitral stenosis or atresia

3. Associated defects not necessarily affecting the usual pressure and blood flow relationships across the interatrial septal defect.
   a. Interventricular septal defect (high pressure communication and left-to-right shunt) (Figure 7)
   b. Mitral or tricuspid valve incompetence

Again, time does not permit a detailed discussion of the exact contributions of the electrocardiogram in each of the foregoing situations. On the basis of the general principles already stated, however, it would seem well to conclude these brief remarks by relating the clinical value of electrocardiography to that of other available diagnostic procedures, especially in interatrial septal defect.

In the so-called "typical" case of interatrial septal defect, with a moderate volume of left-to-right shunt but no significant elevation of pulmonary artery or right ventricular pressures, an accurate diagnosis can usually be made from a combination of physical, roentgenologic, and electrocardiographic signs:

Physical (Auscultatory)
- Basal systolic murmur of pulmonary flow or dilatation
- Apical third heart sound
- Prominent splitting of the pulmonary second sound

X-ray
- Increased volume of pulmonary blood flow
- Dilatation of the pulmonary artery and right atrium
- Right ventricular enlargement +—

Electrocardiogram
- Right bundle branch block +—right ventricular enlargement.

In the case of an interatrial septal defect in which the volume of shunt is small because of the small size of the defect rather than a decreased pressure gradient (from left to right), it is probable that the diagnosis might frequently be missed by clinical examination and made only by direct demonstration, i.e., by cardiac catheterization.

If, because of increased pressures on the right side of the heart, the volume of blood flow through an interatrial septal defect is decreased or its direction reversed, the electrocardiogram may be expected to reflect the underlying hemodynamics (and resulting cardiac anatomy) by displaying evidence of right ventricular hypertension and hypertrophy (in the case of primary or secondary pulmonary hypertension or pulmonary stenosis, or left ventricular hypertrophy in the case of a total right-to-left shunt as in tricuspid atresia). The existence of shunt reversal may, of course, be inferred from the presence of visible cyanosis (or measurable systemic arterial oxygen unsaturation); its location must be demonstrated by either cardiac catheterization or venous angiocardiography.

In differentiating an interatrial from an interventricular septal defect, or in determining the presence of a combined interatrial and interventricular septal defect, direct measurement of the position, direction, and volume of the shunt by cardiac catheterization is generally considered essential. However, physiologic-anatomic information gained from the electrocardiogram (multiple unipolar precordial leads) may be exceedingly helpful — either serving as a guide toward determining the type of information which should be sought in other more technical diagnostic procedures, or in the clarification of physiologic data which for one of several reasons might otherwise be equivocal (ex.— interventricular septal defect with tricuspid insufficiency).

It is worthy of emphasis that electrocardiography is a procedure of absolutely no risk, requiring a minimum of technical equipment and trained personnel, yet capable of providing a wealth of physiologic and anatomic information relative to single and combined cardiac chamber work and size — much more detailed information, in fact, than has been generally appreciated.

THE CLINICAL VALUE OF THE PLASMA ACETONE TEST

FRED W. WHITEHOUSE, M.D.*

Diabetic ketoacidosis is always a medical emergency. In the best institutions, the mortality is still five to ten percent. Early diagnosis and vigorous treatment with insulin and fluid are mandatory to the restoration of metabolic balance. Accurate assessment of the degree of ketosis will aid the clinician in judging the severity of the individual case and in planning adequate replacement therapy.

The determination of the degree of ketonemia is the best method of estimation of the severity of ketosis. While the quantitative method is accurate, it is also time-consuming, and speed is important in the early hours of the management of ketoacidosis. Duncan[1,2] has emphasized the value of the qualitative determination of ketonemia in the diagnosis and management of diabetic ketoacidosis. A more widespread familiarity with this simple test is warranted.

TECHNIC

Two milliliters of either plasma or serum is obtained from the patient at the time of the initial venipuncture. The sodium nitroprusside test for ketone bodies is used, employing either Acetest tablets (Ames Co.) or Acetone test powder (Denver Chemical Co.). Both of these commercially available preparations are quite satisfactory. A series of four test tubes is set up for serial dilution of the plasma or serum with water or normal saline, using respectively, (1) undiluted plasma, (2) one drop of plasma in one drop of diluent, (3) one drop of plasma in three drops of diluent, and (4) one drop of plasma in seven drops of diluent. Then, one drop from each tube is placed upon the reagent and the intensity of color change is recorded in thirty to sixty seconds. This is compared with the standard color chart. The reaction is graded negative to 4 plus.

Under normal conditions, there is no demonstrable ketonemia by this test. The reagent in question is specific for ketone bodies, and no false positives or false negatives have been recorded. While diabetes mellitus is the outstanding condition causing ketosis, starvation, malnutrition and other states associated with increased fat metabolism result in ketosis. The distinguishing feature between the latter and diabetic ketoacidosis is the degree of ketonemia, being many-fold greater in the patient with diabetic ketoacidosis.

With adequate renal function, rapid clearance of ketone bodies from the plasma will occur, giving rise to marked ketonuria without significant ketonemia. This may occur early in the development of ketoacidosis. The currently available "powder" tests for acetone are extremely sensitive and will detect minute amounts of acetone in the urine. Hence, only the determination of plasma acetone will accurately supply the information essential for the proper assessment of the degree of ketosis. Figure 1 illustrates the physiologic progression of acetonuria and acetonemia in diabetic ketosis.

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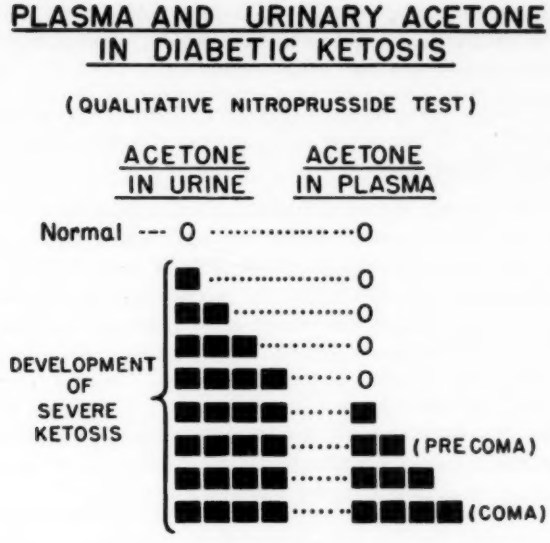

Figure 1

Plasma and Urinary Acetone in Diabetic Ketosis (Qualitative nitroprusside test). A reproduction of Figure 2 in Duncan, G. G., and Gill, R. J.: Clinical value of a simple qualitative test for plasma acetone in diabetic coma, Diabetes 2:353, 1953.

The following case reports exemplify the value of the plasma acetone test in diagnosis and management.

Case 1. M.W., a 32 year old white female with known diabetes of twelve years' duration was seen in the emergency room with a history of nausea and vomiting of two days' duration. There was minimal dehydration, and the vital signs were normal except for hyperpnea. The blood sugar was 380 milligrams percent and the CO_2 combining power was 11 milliequivalents. The urinalysis showed 4 plus glycosuria and acetonuria. The plasma acetone test was 2 to 3 plus in the undiluted specimen. Treatment with 90 units of crystalline insulin and 3000 milliliters of intravenous fluid resulted in restoration of metabolic balance. Eight hours later, the blood sugar was 165 milligrams percent and the CO_2 combining power was 20 milliequivalents.

Comment: While the alkali reserve was moderately depressed, the clinical state and the degree of acetonemia supported early ketoacidosis. Relative insulin sensitivity remained, and a small amount of supplementary insulin and fluid corrected the metabolic derangement. The degree of alkali deficit is valueless in assessing the gravity of the metabolic derangement in diabetic ketoacidosis.

Case 2. F.McG., a 35 year old colored male was seen in the emergency room with the classical signs and symptoms of diabetic ketoacidosis. A blood sugar was 550 milligrams percent. The CO_2 combining power was 4.5 milliequivalents. Glycosuria and acetonuria were 4 plus. The plasma acetone test was 4 plus in the undiluted

specimen and in the first tube dilution. Treatment included 500 units of crystalline insulin and 6000 milliliters of intravenous fluid over an eighteen-hour period. There was a satisfactory recovery from the ketoacidosis.

Comment: Severe ketoacidosis with insulin resistance was accurately assessed early by the knowledge of the degree of ketonemia.. Vigorous therapy corrected the metabolic abnormalities promptly.

Case 3. R.M., a 33 year old white female was admitted to the in-patient department with the complaint of shortness of breath and drowsiness. The patient had known diabetes for sixteen years. Glycosuria on admission was 4 plus, and acetonuria was 2 plus. The blood sugar was 500 milligrams percent, and the CO_2 combining power was 2.9 milliequivalents. The plasma acetone test was negative to trace. Later, a non-protein nitrogen was 188 milligrams percent. The diagnosis was renal acidosis secondary to diabetic nephropathy. Insulin sensitivity remained. Treatment consisted of fluid replacement with sixth-molar lactate solution and small amounts of crystalline insulin over a twelve-hour period. Adequate control of the hyperglycemia was obtained with 75 units of crystalline insulin. Death occurred three days later of uremia.

Comment: The patient was admitted semi-comatose with Kussmaul respirations and standard laboratory findings consistent with the diagnosis of diabetic ketoacidosis. The absence of significant ketonemia pointed to the correct diagnosis of renal acidosis. Treatment included smaller amounts of insulin and intravenous fluid than would apply to a patient with a similar degree of ketoacidosis. This case emphasizes the real value of the plasma acetone test in the differential diagnosis of acidosis occurring in the patient with diabetes.

Case 4. D.O., a 39 year old colored female, a new patient to the hospital, was admitted on the Obstetrical service because of persistent nausea and vomiting and drowsiness. She was in the thirtieth week of her sixth pregnancy. She had known diabetes of nine months' duration and was following no medical program. On physical examination, there was a tachycardia and a mild hyperpnea. The tongue was moist and the eyeballs firm. Her admission urinalysis showed 4 plus glycosuria and acetonuria. Her plasma acetone test was negative. Later, a blood sugar was 231 milligrams percent and a CO_2 combining power was 14 milliequivalents. Eight hours after 44 units of crystalline insulin and 2000 milliliters of intravenous dextrose and water, she was improved clinically, and the glycosuria was 1 plus and the acetonuria was negative.

Comment: Diabetic ketoacidosis did not exist. Rapid evaluation of the metabolic derangement with the aid of the plasma acetone test permitted prompt institution of corrective therapy. In the pregnant diabetic, early restoration of metabolic balance will help prevent intrauterine fetal death. The pregnant diabetic is vulnerable to ketosis and acidosis.

DISCUSSION

The use of the plasma acetone test is of great value in the proper assessement of the acutely ill diabetic patient. In the patient with glycosuria and clinical signs of diabetic ketosis, the finding of significant acetonemia establishes the diagnosis of diabetic ketoacidosis. No other clinical condition gives this combination of clinical and

laboratory findings. The application of the serial dilution technic to this test permits rough quantitations of the degree of acetonemia and accurate estimation of the severity of ketoacidosis. The latter parallels the degree of ketonemia. Renal acidosis in the diabetic patient may simulate ketoacidosis, but can be easily distinguished by the plasma acetone test. Starvation, pregnancy and uncontrolled diabetes may give rise to heavy ketonuria, but can be quickly distinguished from significant ketosis by the use of this test. The difficult differential diagnosis of diabetic ketoacidosis and acute salicylate intoxication has recently been emphasized[3]. The use of the plasma acetone test may have further value by aiding the clinician when this situation arises. Serial plasma acetone determinations may be used in following the progress of the patient with diabetic ketoacidosis. The degree of ketonemia will progressively fall as sufficient insulin is supplied to reconstitute carbohydrate metabolism.

SUMMARY

The plasma acetone test is a simple, rapid and accurate method of determining the degree of ketonemia and the severity of ketosis. It is invaluable for the early diagnosis of diabetic ketoacidosis, and in the differentiation of other conditions simulating ketoacidosis. Familiarity with this test will aid the clinician in the proper assessment of the acutely ill diabetic patient.

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PRELIMINARY REPORT ON THE USE OF A PRESSURE GRADIENT, ELASTIC SUPPORT IN CONDITIONS ASSOCIATED WITH IMPAIRED VASCULAR RESERVE*

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The fundamental bases of the vascular insufficient state can be predicated on any admixture of inherited, anatomic, physiologic and pathologic considerations.

These facets and their interrelationships were developed through a series of lantern slides which stressed the dynamic principles involved in the lymphatic, hemal and tissue pressures associated with this problem. Because the post-thromobophlebitic state is the most common antecedent to vascular insufficiency of the lower extremity, it was used as the model on which to affix the pertinent points of reference. Basically, most of the information available on this problem comes from Burch's primer[1] and Franklin's monograph[2]. These sources were supplemented by the more recent advances in the anatomic and physiologic mechanisms associated with lymphatics[3] and stasis pressures[4] and the histologic findings in the healing of grafts over stasis ulcers of the lower extremities[5]. The pathogenetic factors leading to stasis dermatitis and ulceration were then elucidated[6] but actual detailed therapeutic modalities leading to healing of the ulcers were merely mentioned and not discussed.

The problem of providing and maintaining support adequate to neutralize stasis in the lower extremities in the face of lymphatic, hemal and tissue pressures was then discussed. It was pointed out that because gravity forces the body to employ pressure-gradients it is self-evident that in order to reconstitute the most effective and physiologic appliance to correct vascular insufficient states, one must use a prothesis which employs the same principles. The only appliance available at this time which does this is the Jobst stocking. Actually, this prosthesis is a pressure-gradient pump in the form of a fitted stocking. For maximal results it is essential that the ordering physician himself — not his technician — measure for this prosthesis. Furthermore, the physician must determine by history and physical examination which of the available pressures (30, 40 or 50 mm. Hg) this particular patient needs to come closest to correcting for that insufficiency. On follow-up visits the physician must then evaluate the necessity for more or less pressure to be built into the prosthesis and the correctness of the fitting which he has made.

Aids in making a proper measurement were discussed, and it was pointed out that even with experience one could only hope to get the proper pressure and fitting with the first measurement in but 3 out of 4 patients.

Several graphs were then shown via lantern slides which were a compilation of a 50% answer rate to (20 question) questionnaires that were mailed to our first 200

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**Division of Dermatology.

patients to be fitted for this prosthesis in the Dermatology Division. Of this group, about 75% were seen in the clinic to verify their answers objectively.

From this preliminary information which is obviously based on the poorest possible sampling as the investigator and his colleagues were learning how to apply this prosthesis in this group of patients, it is very encouraging to be able to report that those patients who had the most severe vascular insufficient states were able to be controlled about 90 — 100% if on a venous basis and about 75% if on a lymphatic basis.

The majority of the moderately severe and all of the severe patients had tried all types of prosthetic support prior to the use of pressure-gradient Jobsts with partial to no relief of their symptoms.

The possibility of making these measurements for the prosthesis more uniform and easier through instrumentation was noted and some of the areas in need of more research were indicated.

A series of papers will be forthcoming discussing these problems in the near future.

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ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

***GLUTATHIONE METABOLISM IN NORMAL AND INDUCED STATES OF GROWTH. P. D. Bartlett, P. Grimmett, L. Beers and S. Shelata. Biochim. et Biophys. Acta 20:345, 1956.**

Aside from the demonstration of the participation of glutathione in transpeptidation reactions, there appears to be little additional evidence supporting the attractive hypothesis that glutathione acts as an intermediate in the biosynthesis of other peptides and proteins. If the tripeptide is involved as the hypothesis suggests, however, the relative metabolic activity of liver glutathione and total protein nitrogen in rapidly growing immature normal rats, which are actively engaged in the synthesis and accumulation of body protein, might be expected to differ considerably from that in normal adult rats. We have studied this aspect of glutathione metabolism following a 2-hour period of assimilation of intraperitoneally administered N^{15} labeled glycine. The percentage of administered N^{15} found in the nitrogen of liver glutathione isolated from tissue obtained from normal adult rats and from hypophysectomized immature rats is markedly reduced when such animals are stimulated with growth hormone. This appears to be largely due to an increase in the size of the metabolic pool of liver glutathione. The relatively low percentage of administered N^{15} found in the nitrogen of liver glutathione obtained from rapidly growing immature normal rats compared with that obtained from normal adult rats, on the other hand, can be accounted for only partially in terms of the dilution effect of a larger metabolic pool of glutathione. The N^{15} enrichment of the nitrogen of total liver proteins of rats in normal or induced states of growth, during the 2-hour period of assimilation of the N^{15} glycine, is not significantly different from that observed in rats in which the growth process has been arrested.

***EFFECTS OF B-SITOSTEROL ON REGRESSION OF CHOLESTEROL ATHEROSCLEROSIS IN RABBITS. W. T. Beher, W. L. Anthony, and G. D. Baker. Circulation Research 4:485, 1956.**

To study the effectiveness of B-sitosterol on the regression of cholesterol atherosclerosis, 30 female albino rabbits were maintained on a stock diet supplemented with 1% cholesterol. At the end of 3 months, 10 rabbits were sacrificed, and the remaining 20 rabbits divided into two groups for regression study. One group received the stock diet; the other received the stock diet plus 2.5% B-sitosterol. At the end of a 4-month period, the rabbits were sacrificed, and samples of liver, aorta, and blood removed for evaluation. The data obtained from the determinations, showed: (1) B-sitosterol increased the rate and degree of plasma cholesterol regression; (2) During the development of atherosclerosis, liver cholesterol reached very high levels, which regressed to near control values in four months; (3) At the end of the 4-month treatment period, there was no evident aorta lipid, cholesterol or plaque regression in either of the groups — B-sitosterol treated or control.

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*From Edsel B. Ford Institute for Medical Research.

THE DIAGNOSIS OF POSTCHOLECYSTECTOMY BILIARY TRACT STONES; A COMPARISON OF BILIARY DRAINAGE AND INTRAVENOUS CHOLANGIOGRAPHY. M. A. Block, B. E. Brush, J. L. Ponka and R. J. Priest. A.M.A. Arch. Surg 73:694, 1956.

Diagnostic transduodenal biliary drainage will give positive evidence of postcholecystectomy biliary lithiasis in about one-half of the cases in which stones are actually present. A positive test is definite evidence that stones exist, but a negative test is not significant clinically. The presence of significant abnormalities in the extrahepatic biliary tract shown by intravenous cholangiograms is usually confirmed at subsequent surgery. The value of this examination is limited in that it is not satisfactory for diagnostic purposes in a number of patients with postcholecystectomy symptoms. Both diagnostic transduodenal biliary drainage and intravenous cholangiography are of real value in the evaluation of the problem patient with postcholecystectomy symptoms. Both have distinct advantages and also limitations. The two tests are complementary, and each has an important place in diagnosis. These tests are only aids and are to be used to supplement the sound clinical evaluation of the patient with postcholecystectomy symptoms.

PARAPLEGIA FOLLOWING GENERAL ANESTHESIA. J. W. Ditzler, and G. McIver. Current Res. Anesth. & Analg. 35:501, 1956.

A case is reported of an elderly patient who suffered permanent flaccid paraplegia after general anesthesia and probably attributable to a period of serious hypotension and pre-existent arteriosclerotic disease of the anterior spinal artery. Also presented is a review of literature indicating other cases of paraplegia after general anesthesia. It is suggested that the anatomic location and source of supply for arterial blood to the spinal cord may account for these unfortunate sequelae.

THE MECHANISM OF INTESTINAL PERFORATION FROM NONPENETRATING ABDOMINAL TRAUMA. T. Geoghegan, and B. E. Brush. A.M.A. Arch. Surg. 73:455, 1956.

Perforation of the bowel from trauma to the intact abdomen occurs with sufficient frequency that most surgeons personally encounter several cases. The high mortality rate, 61% of all reported cases between 1935 and 1942, hinges upon delay in operative intervention and closure of the perforation. In our series, when the interval between injury and operation was greater than 12 hours, 4 of 6 patients died; whereas, only 2 of 14 died when the interval was less than 12 hours. Certain characteristics of the lesion itself hinder early operation and closure. These characteristics are the size of the lesion, its location, and the apparently insignificant trauma which is sometimes involved. An analysis of 20 patients is given. Experimental observation of the abdominal contents after external injury is reported on ten dogs. Beside the need for early operative intervention in cases of nonpenetrating traumatic intestinal perforation, we wish to stress the importance of searching for small bursting lesions by careful inspection of both sides of the small bowel throughout its length, as well as the more obvious areas of lacerated bowel and torn mesentery.

DIFFERENTIAL DIAGNOSIS OF COLLAGEN DISEASES. JACK S. GUYTON. A.M.A. Arch. Ophthal. 56:563, 1956.

This paper summarized the differential diagnosis of six syndromes typically classified as collagen diseases. The relative incidence of these was given as follows: Rheumatoid arthritis 90, rheumatic fever 22, lupus erythematosis 4, periarteritis nodosa 3, dermatomyositis 1, and scleroderma 1. The collagen diseases are characterized by widespread focal lesions of connective tissue. They differ individually as to sites of predilection, and there are quantitative histopathological differences in the lesions. However, there is sufficient overlap that at times two or more collagen diseases appear histologically and clinically indistinguishable in their manifestations. This is more likely during early stages than later. Even more commonly, initial manifestations more or less characteristic of one collagen disease (e.g., rheumatoid arthritis) may evolve into those typical of another (e.g., lupus erythematosus). It is seldom difficult to relegate a full-blown collagen disease into its specific niche after observing its course long enough, although occasionally several years of observation may be required for certainty. Each syndrome is described with attention to its most important symptoms and signs.

THE HUMAN SIDE OF ORAL SURGERY — AN EDITORIAL. FRED A. HENNY. J. Oral Surg. 14:347, 1956.

Volumes have been written about the technical aspects of oral surgery with little attention devoted to the humane aspects of patient care. There is, of course, continuing need for technical improvement, but more emphasis should be placed on patient management and public relations. Since it is well recognized that most people are fearful of the various surgical procedures that are carried out in a routine oral surgery practice, it is well to recognize this with adequate sympathetic understanding of their position. All auxiliary personnel should function, not only with efficiency, but with a degree of charm and compassion that is commensurate with the physical and mental trauma that the patient must endure. Efficient expertly administered local or general anesthesia followed by postoperative sedation are, of course, imperative. Clean, Attractive modern surroundings are also of great importance if an optimum end result is to be attained.

CLINICAL VALUE OF THE RODENSTOCK REFRACTOMETER. F. I. HOBBS AND R. A. SCHIMEK. Am. J. Ophthal. 42:59, 1956.

The accuracy and practicality of refraction with the Rodenstock Refractometer has been evaluated. This objective method has been compared to the customary subjective methods of manifest and cycloplegic refractions. Four hundred and seventy-nine eyes of 242 patients were refracted by the three different methods, representing a total of 1226 refractions (on some patients either the cycloplegic or the manifest refraction was omitted). The results have been recorded in graphic form. The non-cycloplegic Rodenstock refractions agreed closely with the customary manifest refraction and the cycloplegic refraction. A Rodenstock refraction had a lower average error due to accommodation in comparison to the cycloplegic refraction than did the average manifest refraction, but large errors in refraction may sometimes occur with the

Rodenstock Refractometer. There are also valid criticisms of the practicality of the Rodenstock Refractometer.

THE EFFECT OF NYSTATIN ON EXPERIMENTAL CANDIDIASIS IN TISSUE CULTURE. FUNAN HU. J. Invest. Dermat. 27:25, 1956.

The result of the present tissue culture study indicates that Nystatin, under the conditions of the experiment, fulfills the requirements of a good *in vitro* antimonilial agent; i.e., it inhibits proliferation of C. *albicans* at concentrations of 50 units and probably kills the organisms at 100 units per ml. of culture medium; and it produces no harmful effects on human epidermal cells at these concentrations. It has a considerable margin of safety. It begins to produce toxic effects on epithelial cells at concentrations higher than 500 units and does not cause complete injury until a concentration of 5000 units is reached.

THE MENOPAUSE AND MYOCARDIAL INFARCTION. T. N. JAMES, H. W. POST AND F. J. SMITH. J. Am. Geriatrics Soc. 4:797, 1956.

Myocardial infarction is rare in women of premenopausal age and rarer in such women without diabetes mellitus, hypertension or systemic disease affecting blood coagulation or blood vessel structure. This is in striking contrast to men of comparable age in whom myocardial infarction, due to spontaneous atherosclerosis, is not at all uncommon. Records were reviewed of 146 women admitted consecutively to the hospital with myocardial infarction. The average age at menopause in 108 of these patients was 47.4 years, and the average interval between the time of the menopause and the time of the initial attack of myocardial infarction was 16.6 years. The discussion is devoted primarily to the effect of estrogens on cholesterol metabolism and experimental atherosclerosis. Estrogens, however, do have other important effects through their influence on vascular tone, electrolyte metabolism and constitutional development.

NOTE ON CALCIUM ION REQUIREMENTS FOR THREONE ACTIVITY. SHIRLEY A. JOHNSON AND W. H. SEEGERS. Proc. Soc. Exper. Biol. & Med. 92:597, 1956.

When purified prothrombin was activated by platelet cofactor I (antihemophilic factor) and platelet factor 3 the optimum calcium concentration ranged from 0.009 M to 0.04 M. This is a much broader optimum range than that found when tissue thromboplastin (lung extract) activated purified prothrombin.

EPIPHYSIOLYSIS. J. A. JOHNSTON, G. MANSON AND C. L. MITCHELL. A.M.A. J. Dis. Child. 92:337, 1956.

The pathogenesis of epihysiolysis is reviewed, and the theory most tenable on the basis of studies to date discussed. Seven balance studies on epiphysiolysis patients are presented, six of which show subnormal calcium retentions and serum phosphorus levels. In four cases in which it was employed, adequate vitamin D is shown to increase calcium retention significantly. The concept that epiphysiolysis is a disease preventable by proper nutritional practice is emphasized and specified dietary regimens are suggested.

NUTRITION AND TUBERCULOSIS IN THE ADOLESCENT. J. A. JOHNSTON. Am. Rev. Tuberc. 74:173, (Aug. Pt 2) 1956.

In twenty-five year follow-up study of 1100 tuberculin reactors there were discovered 39 reaction type cases. Of these, 29 were considered to have developed endogenously years after their removal from contact. A majority of these occurred in adolescence. Balance studies for nitrogen and calcium revealed excellent correlation between healing and the adequancy of nitrogen storage. A variety of conditions influencing nitrogen storage were explored, including the nitrogen requirement, focal infection, a number of the hormones, rest, and activity. It was shown that anything which affected adversely the storage of nitrogen was followed by spread or failure of healing of the tuberculous lesion; conversely healing regularly followed adequate storage even before the advent of the newer chemotherapeutic agents. A depressed retention of nitrogen immediately following the menarche in girls was considered to be one of the factors causing reactivation.

SURVIVAL RATES AFTER ACUTE MYOCARDIAL INFARCTION WITH LONG-TERM ANTICOAGULANT THERAPY. J. W. KEYES, E. H. DRAKE AND F. J. SMITH. Circulation 14:254, 1956.

A study of myocardial infarctions, both single and recurrent, compared 234 control cases to a similar group of 121 cases treated with anticoagulants and followed over a five year period. Statistical analysis of the data by mean life estimate determinations showed:

1. Single infarct cases. The rate of death was three times greater in the control than in the treated group. The mean life estimated was 83 months in the control group and 292 months in the treated cases.

2. Recurrent infarct cases. The death rate was five times greater in the control group than in the treated group. The mean life estimate was 39 months in the control group and 204 months in the treated group.

Bleeding occurred, over a five year period in minor or major degree, 54 times in 51 patients (42.1%). In the last two years of the study, however, it was reduced to less than 2%. Major bleeding occurred in 16 cases (13.2%) with three deaths attributed indirectly to hemorrhage. The hazard from bleeding is considerably less than the risks of the disease itself, when one considers that at the end of two years 27.9% of the single infarct cases and 39.6% of recurrent infarct cases were dead, compared to 5.6% and 8.0% respectively of the treated group. At the end of four years 41.4% and 62.5% of the single and recurrent cases respectively were dead, compared to 8.4% and 12% in the anticoagulant group.

DERMATITIS IN INFANTS AND CHILDREN. C. S. LIVINGOOD AND E. M. SHAPIRO. Pediat. Clin. North America. 3:741, 1956.

A dermatitis is a simple inflammation of the skin and is the commonest of all skin conditions. The various types of dermatitis seen in infants and children although confusing may be separated into fairly distinct clinical entities. A brief and simplified

classification is presented as an aid to the physician who has not had special training in Dermatology.

The classification of the various types of dermatitis is based on etiology as far as possible, but when necessary, distribution, morphology, history, and course of the eruption are considered. The term "eczema" is confusing and is used only as a qualifying prefix in several conditions.

The conditions discussed are: contact dermatitis, atopic dermatitis, seborrheic dermatitis, nummular eczema, lichen simplex chronicus (localized neurodermatitis), and eczematous dermatitis. A clinical description with appropriate photographs and a rational method of treatment of each of these conditions is presented.

RESPIRATORY INFECTIONS DUE TO KLEBSIELLA PNEUMONIAE. G. L. Morris, and J. L. Yates. Dis. Chest 30:298, 1956.

The current literature and the case histories of 10 patients with varying degrees of respiratory illness from whom K. pneumoniae was isolated are reviewed. The following points have been derived: Predisposing diseases are important in the etiology of Friedlander's pneumonia. Six of our patients had diabetes. Isolation of Friedlander's basillus from a patient with pulmonary disease does not prove causal relationship. Early bacteriological diagnosis is important. Combined therapy with penicillin and streptomycin was ineffective in this series. The best antibiotic regimen is probably streptomycin plus a broad spectrum antibiotic. Chronic Friedlander's pneumonia may resemble tuberculosis or carcinoma. The use of nor-epinephrine and/or cortisone may be lifesaving as supplemental therapy for acute overwhelming pneumonias.

*MAGNESIUM DIBASIC PHOSPHATE IDENTIFIED AS A CRYSTALLINE COMPONENT OF A URINARY CALCULUS. Jonathan Parsons. J. Urol. 76:228, 1956.

Magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4.6H_2O$) is found as a constituent of urinary calculi being commonly associated with alkaline infected urine. This crystalline material often occurs mixed with one of several complex calcium phosphate compounds commonly called by general name apatite. This paper deals with the finding of a previously unreported constituent, magnesium dibasic phosphate ($MgHPO_4.3H_2O$). Comparative photographs of the x-ray diffraction patterns of the renal calculus and a chemically pure standard of magnesium dibasic phosphate confirm the tentative identification made from preexisting photographs. The crystalline interplanar spacing data pertinent to future identification of this compound are also given.

*STEROID X-RAY DIFFRACTION POWDER DATA. J. Parsons, W. T. Beher and G. D. Baker. Anal. Chem. 28:1514, 1956.

This is the third in a series of papers publishing x-ray diffraction patterns and molecular interplanar spacings for the organic compounds known as the steroids. Data and photographs for 40 compounds are included in this report bringing the total thus far studied and reported upon to 106 steroid compounds.

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THROMBOCYTOPENIA AND HEMORRHAGE IN HEMOLYTIC BLOOD TRANSFUSION REACTIONS. PAUL W. PIFER, M. A. BLOCK AND C. P. HODGKINSON. Surg., Gynec. & Obst. 103:129, 1956.

Heterologous blood was administered to dogs and rabbits in varying quantity and rates of flow in fifteen experiments. Intravenous administration of heterologous blood experimentally resulted in an abnormal bleeding tendency similar to that observed in hemolytic blood transfusion reactions in man. A critical precipitous fall of blood platelets and a small decrease in plasma fibrinogen are associated with the transfusion reaction. The bleeding time is usually prolonged and frequently the coagulation time is prolonged, but these changes usually are only of several hours duration. It appears that fibrin and platelet emboli or thrombi form in blood vessels throughout the body as a non-specific reaction, such as occurs in a number of conditions in which foreign proteins are present in the blood stream. Thrombocytopenia and hypofibrinogenemia result in a bleeding tendency. In varying situations thrombocytopenia or hypofibrinogenemia may predominate.

INTUSSUSCEPTION DUE TO INVAGINATED MECKEL'S DIVERTICULUM; PRESENTATION OF TWO CASES AND AN ANALYSIS OF FIFTY-TWO CASES COLLECTED FROM THE LITERATURE. JOSEPH L. PONKA. Am. J. Surg. 92:545, 1956.

Fifty-four cases of intussusception due to invaginated Meckel's diverticulum are reviewed. Important symptoms include a sudden onset of severe, cramping, periumbilical pain with vomiting, decreasing bowel movements and passage of blood and mucus. Forty-one of fifty-four patients (77 percent) presented either one or a combination of this triad of findings: an abdominal mass, a rectal mass or rectal blood. Early surgery should be urged but it presupposes early diagnosis which is of the greatest importance. More attention to the state of fluid and electrolyte balance preoperatively will help to improve the results. Surgery in critically ill patients should be withheld until proper hydration is achieved and the chemical balance is at least partially attained. The mortality rates are improving and during the past twenty years fifty-four patients were treated, with a mortality rate of approximately 20 per cent. Seven patients died. The outcome in two cases was not described. This represents a decrease of at least 15 per cent in the death rate of this condition since 1933. Adults with intussusception frequently give a long history of recurring bouts of periumbilical pain; in infants this does not hold true. Surgery is the treatment of choice and warning is given against the use of enemas to achieve reduction, since reduction of the invaginated Meckel's diverticulum cannot be accomplished by this means. A competent ileocecal valve would further complicate the problem by preventing the medium used in the reduction from reaching the terminal ileum.

*STABILIZATION AGENTS IN WELL COUNTING FOR REPRODUCIBLE ASSAY OF RADIOACTIVE COLLOIDS. L. E. PREUSS AND A. VANN. Atomics, Engineering & Technol. 7:260, 1956.

A method is described in which conventional suspension media are used to stabilize colloidal Au-198 specimens for liquid sample well scintillation counting. The technique applies some suspension methods to the systems of radiation detection. The method is rapid, by-passes lengthy digestions, and eliminates sedimentation errors encountered in the well crystal technique. Sedimetation errors are discussed briefly.

HYPOPHYSECTOMY FOR DIABETIC RETINOPATHY; A PRELIMINARY REPORT. ROBERT A. SCHIMEK. A.M.A. Arch. Ophthal. 56:416, 1956.

The adrenal hyperfunction which accompanies and may be a cause of retinopathy in diabetes may in turn be caused by pituitary hyperfunction. Pituitary hyperfunction, in addition, may contribute to diabetes and diabetic retinopathy directly through the diabetogenic factor, the growth hormone and other less well defined principles. Hypophysectomy, therefore, may be of value in diabetic retinopathy in two ways. Furthermore, by removal of the source of corticotrophin, reduction of glucocorticoid secretion is brought about more safely for the patient than by complete adrenal ablation, since, even in the abscence of the pituitary, aldosterone secretion continued at a low level lessens the danger of electrolyte imbalance and shock. In the small series of five cases of diabetic retinopathy in whom hypophysectomy has been performed to date, results are thus far very encouraging, although the follow-up has been too short or the retinopathy too advanced to permit final decision on the value of the operation. These patients have experienced no further loss of vision. Hypertensive blood pressures have declined and repeated hemorrhages into the retina and vitreous humor have ceased. High insulin requirements have been lowered. There have been no deaths from hypophysectomy in our series. The operation is formidable, with a mortality rate of 5% to 10% indicated in the literature. The dangers involved and the probability of not being helped must be explained to the patient. Despite the risk of hypophysectomy and its subsequent requirement of glandular replacement therapy, further trial appears to be indicated. This is particularly true since diabetic retinopathy remains one of the leading causes of progressive incurable blindness.

ABLATION THERAPY FOR THE RELIEF OF MENIERE'S DISEASE. H. F. SCHUKNECHT. Laryngoscope 66:859, 1956.

The various regimens of medical treatment are only partially successful in relieving the vertiginous symptoms of Meniere's disease. When the attacks are so frequent and severe as to incapacitate the patient, ablation therapy should be considered. For the patient with unilateral Meniere's disease this is accomplished simply and effectively by either labyrinthotomy or intra-tympanic streptomycin. Details of the recommended techniques for each of these procedures are described. By either method the hearing which remained in the diseased ear is lost. Ablation therapy, therefore, is usually not recommended unless the threshold loss for speech reception in the diseased ear is at

*From Edsel B. Ford Institute for Medical Research.

least 40 d b, and the speech discrimination score not better than 40%. For patients with incapacitating bilateral Meniere's disease, it is imperative that all existing auditory function be preserved. This is best accomplished by parenteral streptomycin therapy, by which it is possible to create a severe but not total loss of vestibular function in both ears and save hearing.

*INTERMEDIARY METABOLISM OF L-CYSTEINESULFINIC ACID IN ANIMAL TISSUES. T. P. SINGER AND E. B. KEARNEY. Arch. of Biochem. 61:397 1956.

1. Homogenates and soluble extracts of rat liver mitochondrial acetone powder catalyze the rapid, coupled oxidation of cysteinesulfinate (CSA) and fumarate (or malate) to yield pyruvate, aspartate, and inorganic sulfate, as well as an analogous reaction between CSA and a-ketoglutarate to yield pyruvate, glutamate, and sulfate. In preparations from heart mitochondria the same reactions occur, except that the sulfur moiety of CSA accumulates as sulfite.

2. The reactions above have been shown to involve rapid transaminations of CSA with a-ketoglutarate or oxalacetate. B-Sulfinylpyruvate, the product of these transaminations does not accumulate in the preparations but is cleaved to pyruvate and sulfite. The latter is oxidized to sulfate by sulfite oxidase in liver preparations but not by heart mitochondria.

3. The very slow formation of oxalacetate from fumarate or malate by malic dehydrogenase in the mitochondrial system is greatly enhanced by the presence of CSA, by virtue of the rapid and complete removal of oxalacetate in the transamination reaction.

4. Highly purified glutamic-oxalacetic transaminase catalyzes the reaction of CSA and a-ketoglutarate more rapidly than the transamination between aspartate and a-ketoglutarate. It is suggested that the observed transamination of CSA with oxalacetate and a-ketoglutarate may be the result of the action of glutamic-oxalacetic transaminase.

5. Another, apparently non-transaminative, oxidation of CSA to pyruvate, sulfate, and ammonia has been observed in fresh rat liver mitochondrial acetone powders. The reaction is DPN-dependent. It is suggested that the initial steps may be the anaerobic dehydrogenation of CSA by a DPN-linked enzyme to B-sulfinylpyruvate and ammonia and that the further metabolism of the keto acid is identical with that occurring in the coupled reactions described.

6. It is pointed out that these results and other data in the literature confirm the view that the mineralization of the sulfur moiety of cysteine in liver occurs at the oxidation level of CSA and entails cleavage of B-sulfinylpyruvate to sulfite, followed by the action of sulfite oxidase.

7. The central position of transaminations involving CSA in the interrelations of carbohydrate and sulfur metabolism is discussed.

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*From Edsel B. Ford Institute for Medical Research.

*FINE STRUCTURE OF SUBMICRON IRON PARTICLES. J. H. L. WATSON AND M. W. FREEMAN. Kolloid-Zeit. 148:3, 1956.

High resolution electron micrographs of samples of colloidal alpha iron are shown. According to prescribed conditions the samples occur as (1) particulates (with potential application in medicine) with mean diameters 900 angstrom units and less, (2) large, well-formed dendrites useful wherever strength of the dendrite is a desirable quality, (3) shorter, more fragile dendrites, (4) serrated or nodular rods and/or (5) needles. Materials of types 4 and 5 are particularly valuable for magnetic purposes and on test demonstrate intrinsic coersive forces of more than 1650 oersteds. The central stems are a line of single iron crystals which are 100 to 500 angstrom units in diameter. A fine laminar structure is often observed in the single crystals and some of the secondary branches. These appear to be 40 to 50 angstrom units thick with 20 to 25 angstrom units between the layers. The same laminar structure is often observed in large, hexagonal platelets which occur in some samples. Stereoscopic studies show that the dendrites are three dimensional with their branches and main stem not in the same plane. X-ray diffraction detects alpha iron plus some form of Fe_2O_3 in most samples.

*SHADOW CASTING OF TISSUE SECTIONS FOR ELECTRON MICROSCOPY. J. H. L. WATSON. Lab. Invest. 6:451, 1956.

The electron microscopy of shadow-cast, ultra thin tissue sections from which the embedding has been partially removed by electron bombardment is considered. The effects of heat, coupled with those caused by action of electrons upon the molecules of embedding material, are discussed with reference to removing the embedding plastic, and the phenomenon of "electron fixation" is mentioned. The advantages of shadow-casting sections from which the embedding has been partially removed are illustrated by a thin section of mouse testis and a thick section of hair cells from the utricle of the cat.

DIABETES AND PREGNANCY. F. W. WHITEHOUSE, W. L. LOWRIE, AND C. P. HODGKINSON. J. Michigan M. Soc. 55:1211, 1956.

Sixty-one pregnancies in forty diabetic mothers have been reviewed. After viability, there is a fetal salvage of 68.8 per cent in our series. The incidence of preeclampsia is 37.7 per cent, polyhydramnios 20 per cent, and ketoacidosis 19.7 per cent. The fetal survival was adversely affected by the last but not by the first two. Early timed delivery has been practiced during the time covered by this study. The overall fetal survival using caesarean section is 88 per cent. Assiduous diabetic control and prenatal care followed by early timed delivery employing caesarean section appears to be the plan of management most likely to result in a successful outcome in the average case. The role of female sex hormones is controversial, but they probably should be used in selected cases. Sterilization and interruption of pregnancy in the average case are not indicated. Only by close co-operation between internist, obstetrician and pediatrician will the present tragic fetal loss be eradicated.

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*From Edsel B. Ford Institute for Medical Research.

THE IMPORTANCE OF POSITIVE T WAVES IN THE RIGHT PRECORDIAL ELECTROCARDIOGRAM DURING THE FIRST YEAR OF LIFE. R. F. ZIEGLER. Am. Heart J. 52:533, 1956.

T waves are normally positive in right precordial leads only during the first twenty-four hours of postnatal life and then in a small percentage of cases after the first decade. There is a direct correlation between the incidence of positive T waves in right precordial leads and elevation of right ventricular mean pressure, hypothetical in the case of the normal newborn, proved numerically in cases of pathologic right ventricular hypertrophy after the first day of life. Three precordial lead patterns are described which, in infancy at least, correspond within certain limits to progressive degrees of right ventricular hypertrophy. The first is represented by a single-peaked RS deflection of normal measurements, followed by a positive T wave in leads from the right side of the precordium. The second is represented by the superimposition on the former pattern of right bundle branch block, in which the detection of pathologic right ventricular hypertrophy is certain from the configuration of QRS, but with inverted T waves in leads from the right side of the precordium. The third is represented by an R wave of 100 per cent amplitude (of RS), frequently preceded by a true initial Q wave, and followed by a positive T wave in right precordial leads. A fourth pattern which has been discribed is represented by the so-called "barrage" type of Donzelot, with right ventricular potential variations (of right ventricular hypertrophy plus right bundle branch block) extending across the entire precordium. With QRS or T-wave evidence of right ventricular hypertrophy in right precordial leads, the occurrence of T-wave inversion in leads from the left side of the precordium, with or without the administration of digitalis, constitutes strongly presumptive evidence of associated left ventricular hypertrophy, if these leads (V_5 or V_6) represent the potential variations derived from the epicardial surface of the left ventricle. In infants with electrocardiographic evidence of predominant left ventricular hypertrophy, the presence of positive T waves in right precordial leads is considered evidence of associated right ventricular hypertension (and probably hypertrophy) if the amplitude of R in Lead V_1 equals or exceeds 40 to 50 per cent of the total amplitude of RS in the same lead. The probability of this sign indicating associated right ventricular enlargement decreases as the R wave amplitude in Lead V_1 decreases to 20 or 30 per cent or less of the total amplitude of RS in this lead. The observations reported herein, and their significance, are not necessarily limited to the period of infancy. However, in order to establish accurate diagnostic criteria for older children and adults, separate numerical criteria will have to be established for each successive age group.

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